

**UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION**

**IN RE NATIONAL PRESCRIPTION
OPIATE LITIGATION**

This document relates to:

Track Three Cases

MDL No. 2804

Case No. 17-md-2804

Judge Dan Aaron Polster

**DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY
DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS
AND TESTIMONY OF DR. KATHERINE KEYES**

EXHIBIT 4

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EXPERT REPORT OF KATHERINE KEYES, PhD

December 19, 2019

In Re Opioid Litigation, 400000/2017

Relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018

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(ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at a range of 96 mg per person in 1997, and increased to 700 mg per person by 2007 (greater than 600% increase).^{12,13} In 1995, the year OxyContin entered the market, the number of opioid prescriptions filled in the United States increased by 8 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2010 at 62 million prescriptions dispensed.^{14,15} From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670,000 in 1997 to about 6.2 million in 2002.¹⁶ The increase in opioid prescribing was driven by a multitude of factors, including direct marketing to physicians using data that underestimated opioid use disorder risks in patients, which I will detail in Section B. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future.^{17,18} That is also true for prescription opioids; as a result, increasing marketing of opioid drugs led to increased sales of the marketed drugs.^{19–21}

As discussed in detail below, based on the available evidence, including multiple studies, the rapid increase in total opioid prescribing levels after the introduction of OxyContin in 1996 correlates with marketing of opioids to physicians which downplayed the risks of harms associated with prescribing, including opioid use disorder and overdose.

Evidence published in 2019 indicates that the number of opioid prescriptions filled has declined in recent years,²² and yet the number of opioid prescriptions filled remains high—and significantly higher than it was in the mid-1990s. Data from outpatient prescribing records from IQVIA Xponent database, covering 59,400 pharmacies (representing 92% of retail prescriptions dispensed in the United States) reflects trends from 2006 through 2017 in milligrams of prescribed opioids, duration per prescription, high dosage prescription fills (defined as a dosage equal to or greater than 90 MMEs per day), prescriptions filled for 3 days or fewer and 30 days or longer, and extended-released/long-acting formulation prescriptions. While there are overall declines in opioid prescribing, and high dose prescribing, the volume of opioids prescribed remains high and prescription length continues to increase. Opioid prescriptions per person in the total United States increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In 2017, there remained a high level of opioid prescribing in the United States, with 191,218,266 prescriptions dispensed, leading authors to conclude that still in 2017 “pharmacies filled enough opioid prescriptions to theoretically provide every US resident with 5 mg of hydrocodone bitartrate every 4 hours around the clock for 3 weeks.”²² Hydrocodone bitartrate has several formulations, including hydrocodone bitartrate with acetaminophen commonly known as Vicodin. Focusing on New York in particular, evidence indicates that from 2006 through 2010, the increase in MME per person was higher than the national average, with an annual percentage increase of 8.7% (nationally the average annual increase was 6.9%); from 2010-2015, MME per person in New York State decreased 2.7% (nationally, the average annual decrease was 3.8%, indicating a slower decrease in New York State compared to the United States average), and from 2016-2017, the average annual decrease was 11.2% (closer to the national average annual decrease of 10.7%).²² These dynamics over time are also apparent within Nassau and Suffolk Counties. Based on IQVIA data published by county by the CDC,²³ the opioid prescribing rate in Nassau County increased from 46.0 to 51.1 prescriptions per 100 persons from 2006 to 2011; thereafter, prescribing decreased similarly to the rest of New York State, with the rate per 100 persons of 36.0 in the most recent year of data available, 2017. In Suffolk County, prescribing increased from 61.0 per 100 persons to 70.2 prescriptions per 100 persons in 2011. Thereafter prescribing declined similarly to the national and New York State overall, to 45.4 per 100 persons in 2017.

B. Risks of opioid use disorder following medical use of prescription opioids follow a “dose-response” pattern

Early studies cited in marketing materials to physicians underestimated the addiction potential of prescription opioids, and included claims that risks of opioid use disorders are rare among those prescribed opioids. Much of the material provided to physicians on the risks of opioid use disorders after medical prescription of opioids, however, was based on studies that were inadequate epidemiologically, such as Porter and Jick (1980),²⁴ which did not examine risk of use disorder or dependence based on dose or length of use of opioids, and did not use validated or objective assessments of opioid use disorder. Further, the doses,

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1.32 to 1.53 per 1,000 births,^{101,102} Nassau County information is consistent with the instrumental variable analysis that suggests a causal role for opioid supply on opioid related harm.

The supply of opioids was also facilitated by pharmaceutical promotional activity to physicians. While I did not evaluate the specific marketing materials of the manufacturers, I did evaluate peer-reviewed epidemiological studies that document the association between marketing with sales, which is germane to my expertise. Epidemiological evidence using statistical methods is routinely used to assess the association between exposure to pharmaceutical marketing and sales efforts with changes in prescribing, and has reliably found across many studies in many populations that exposure to pharmaceutical marketing and sales is significantly associated with increases in prescribing of the marketed drugs. Indeed, available epidemiological evidence using rigorous quasi-experimental designs, such as difference-in-difference models, as well as controlling for numerous potential confounders, has consistently documented an association between the industry payments, meals, sales outreach to physicians, as well as pharmaceutical promotions, with increases in requests to add specific products to hospital formularies¹⁰³ as well as increases in rates of prescribing the marketed products.^{104–107} These broader literatures provide a consistent evidence base when examining the associations between opioid marketing and opioid sales. Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,¹⁰⁸ and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.^{18,108–110} Hadland et al. (2019)¹¹¹ used data from the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. The authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g., unemployment, income, income inequality), as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose, including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmaceuticals. These results confirm through independent epidemiological analysis that outreach and payments to physicians through the pharmaceutical companies was an important way in which the distribution of opioids across the United States was facilitated.

Finally, a working paper authored by Powell et al. (2015)¹¹² examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of the opioid supply among those aged 65+. This paper is particularly relevant given the quasi-experimental design of using an exposure with exogenous variation, and a new law passed heterogeneously across states, to assess changes in the opioid supply. “Exogenous variation” is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare system cannot be caused by users of that system, and as for that reason, associations between changes in the Medicare system and changes in opioid supply are more likely to be causal. Using data from 1999 through 2016, the authors documented that the Medicare expansion affected the opioid supply, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid supply based on ARCOS data. Further, the authors examined correlations with drug overdose deaths (specifically those with codes that indicate prescription opioid poisoning), as well as substance abuse

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